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Review

Effects of host genetic variations on response to, susceptibility and severity of respiratory infections

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ABSTRACT

The recent outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a global crisis, necessitating the identification of genetic factors that modulate the risk of disorder or its severity. The current data about the role of genetic risk factors in determination of rate of SARS-CoV-2 infection in each ethnic group and the severity of disorder is limited. Moreover, several confounding parameters such as the number of tests performed in each country, the structure of the population especially the age distribution, the presence of risk factors for respiratory disorders such as smoking and other environmental factors might be involved in the variability in disease course or prevalence of infection among different ethnic groups. However, assessment of the role of genetic variants in determination of the course of other respiratory infections might help in recognition of possible candidate for further analysis in patients affected with SARS-CoV-2. In the current review, we summarize the data showing the association between genomic variants and risk of acute respiratory distress syndrome, respiratory infections or severity of these conditions with an especial focus on the SARS-CoV-2.

1. Introduction

The recent pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19) and created a global crisis, devastating health organizations and perplexing researchers to find the solution for this problem. Meanwhile, it has raised the question whether genetic factors can define the susceptibility to the disorder or the severity of symptoms. Although few studies have tried to answer the question [1], it seems to be too early to reach a conclusive results in this regard. Yet, previous studies have indicated that susceptibility to respiratory tract infections is determined by both genetic and acquired risk factors [2]. As SARS-CoV-2 exploits angiotensin converting enzyme 2 (ACE2) for its entrance inside the cells, this gene is a putative risk factor for this infection [3,4]. Being located in a genomic region on chromosome X that escapes from X inactivation, it has a heterogeneous sex bias expression in different tissues [5]. Higher levels of its expression in male tissues has been attributed to 17β-estradiol-dependent and sex chromosome-independent mechanisms [6]. Fig. 1 shows the role of some polymorphisms is *ACE2* and other genes in the course of SARS-CoV-2 infection.

In the current review, we conducted a comprehensive search to find the genetic variants that modify the risk of respiratory tract infections with especial focus on viral infections. We summarize the data showing the association between genomic variants and risk of these infections or severity of the disorder.

2. SARS-CoV

Itoyama et al. have investigated the role of ACE1 insertion/deletion (I/D) polymorphism in conferring risk of SARS or disease course in the Vietnamese individuals. They reported higher frequency of the D allele in the hypoxemic group compared with the non-hypoxemic group. However, there was no remarkable difference in the frequency of these alleles between the SARS-CoV cases and non-affected individuals,

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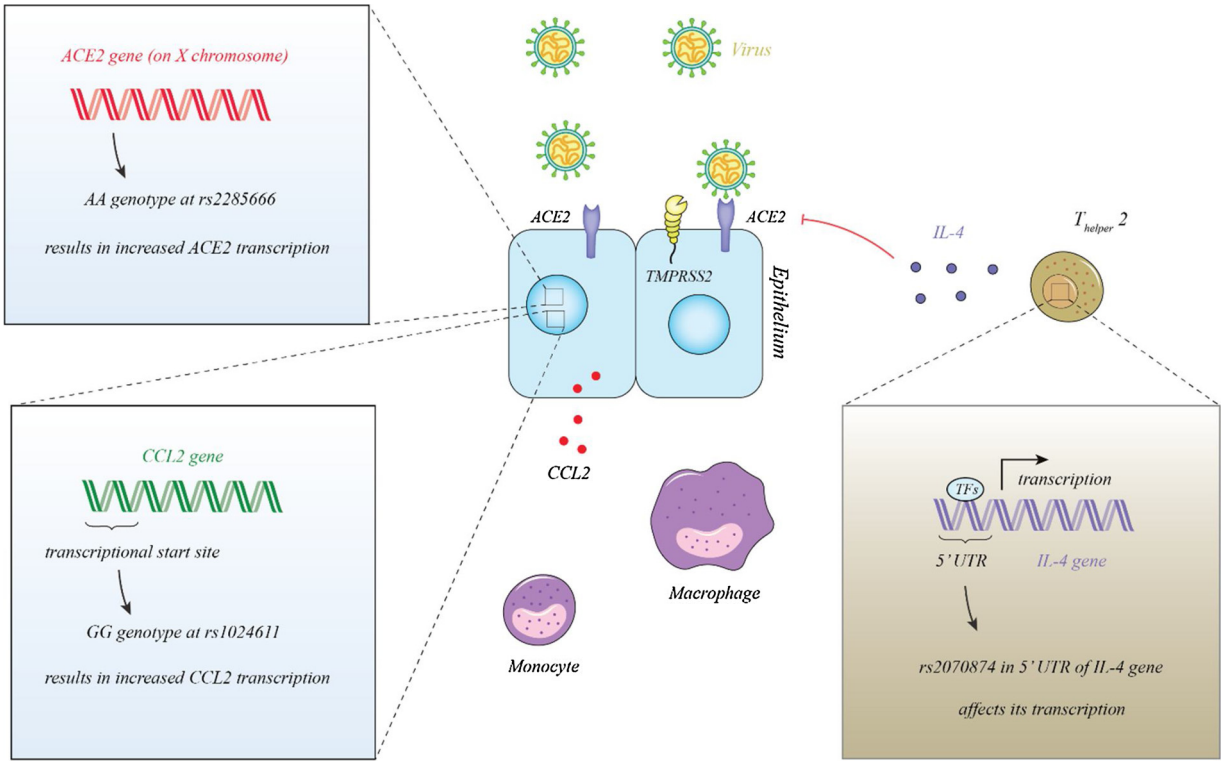

Fig. 1. *ACE2* gene is located on chromosome X, in a genomic region which escapes from X inactivation. Yet, it has a heterogeneous sex bias expression in different tissues [5]. The AA genotype of the rs2285666 is associated with higher expression of ACE2. Based on the role of ACE2 as the cell receptor for entrance of the virus, the mentioned polymorphism might affect the infection course [1]. The rs1024611 is located in the transcript start site of the *CCL2* gene and might affect expression of the corresponding gene. The GG genotype of this polymorphism is associated with higher levels of CCL2. CCL2 is a chemokine that regulates chemotaxis and secretion of inflammatory mediators from monocytes and macrophages [7]. The rs2070874 polymorphism is located in the 5' UTR of *IL-4* gene and might influence transcription of this gene [8]. IL-4 down-regulates ACE2 receptor, thus preclude SARS-CoV entrance into the cells [9].

regardless of the contact history. Thus, ACE1 has been suggested as a candidate locus for determination of the course of SARS in the assessed population [10]. Tu et al. genotyped the *CCL2* G-2518A and *MBL* codon 54 variant (A/B) in four populations of Chinese patients with SARS and healthy subjects. They reported association between the high-CCL2-producing GG genotype and the low-MBL-producing B allele and higher susceptibility to SARS-CoV infection in all cohorts. Yet, there was no association between these variants and severity of SARS [7]. Lau et al. have shown association between the IFN-γ +874A allele and RANTES −28 G allele and risk of SARS-CoV infection. The RANTES −28 G allele has also been shown to participate in the pathophysiology of this infection. However, the assessed SNPs of IL-10, TNF-α, IL-12, IP-10, Mig and MCP-1 were not linked with the risk of SARS-CoV [11]. Yuan et al. have we evaluated a certain SNP in CD14 gene in a population of SARS patients who were formerly genotyped for FcγRIIA SNPs. They found higher frequency of the CD14-159CC SNP and severe SARS. Both CD14-159CC and FcγRIIA-RR131 SNPs were described as susceptibility factors for severe SARS-CoV infection [12]. Based on the previously reported effects of CD209 in the promotion of SARS-CoV spike protein-bearing pseudotype associated infection in permissive cells, Chan et al. have assessed association between a variant within this gene and clinical outcome of patients with SARS-CoV infection. SARS patients who carry the −336AG/GG genotype had lower standardized lactate-dehydrogenase (LDH) levels and poorer outcome compared with the −336AA patients [13]. Besides, Lin et al. have assessed association between HLA alleles and SARS-CoV infection in Asian population. HLA-B*4601 and HLA-B*5401 were reported as the most probable factors in conferring risk of infection, when comparing infected SARS patients and high risk health care workers individuals. The severity of SARS-CoV infection was correlated with HLA-B*4601 [14].

3. SARS-CoV-2

Asselta et al. have recently investigated the putative genetic elements of the strange severity of COVID-19 among Italians. They have observed the transcript levels and genetic polymorphisms in ACE2 and TMPRSS2 genes, which have been shown to be involved in the process of viral infection. They have assessed the data of exome and single nucleotide polymorphism (SNP) array in a large cohort of Italian individuals as an illustrative model of the whole population. Then, they compared the presence of rare variants and the occurrence of SNPs with Europeans and East Asians. Besides, they searched the gene expression catalogues to examine the sex-biased expression. Surprisingly, they detected no remarkable clue for association between ACE2 and COVID-19 severity/sex bias in the Italian population. Yet, expression levels and SNPs of TMPRSS2 were identified as putative modulators of this disorder explaining the reported statistics among Italian patients. Yet, the obtained results should be verified through experimental analyses in large sample sizes of affected individuals with various clinical presentations [1]. Renieri et al. have retrieved the exome data of 7000 individuals from the Network of Italian Genomes to assess the ACE2 variants. They recognized some variants with a potential effect on the stability of the ACE2 protein. Three missense variants with minor allele frequencies between 0.002 and 0.015 were anticipated to alter protein cleavage and stabilization. The variants p.Asn720Asp, p.Lys26Arg, p.Gly211Arg have not been detected in the Eastern Asia population. They also detected rare truncating variants that modulate the internalization course and one missense variant (p.Trp69Cys) which was anticipated to alter the process of SARS-CoV-2 spike protein binding. Although not verified by experimental assays, these SNPs might participate in the detected inter-individual difference in the severity of disorder [3]. Cao et al. have assessed the functional role of 1700 ACE2

Table 1
Summary of studies which reported association between SNPs and host responses to respiratory infections.

Gene	Disease	SNP	Sample	Population	Comment	Ref
TMPRSS2	SARS-CoV-2	rs463727, rs34624090, rs55964536, rs734056, rs4290734, rs34783969, rs11702475, rs35899679, rs35041537, rs2070788, rs9974589, rs7364083	General: 125,748 WES 71,702 WGS, Italian: 3,984 WES 3,284 GWAS	European and East Asian	Two haplotypes were supposed to increase TMPRSS2 expression in an androgen-specific way.	[1]
	Influenza	rs2070788, rs383510	162 severe/ 247 mild	Chinese	rs2070788-GG and rs383510-T confer higher TMPRSS2 expression and disease susceptibility or severity.	[16]
ACE2	SARS-CoV-2	207G > T rs775181355	6984 WES	Italian	p.Asn720Asp, p.Lys26Arg and p.Gly211Arg were predicted to interfere with 2019-nCov spike protein, thus destabilizing the protein structure.	[3]
		rs2285666	General: 125,748 WES, 71,702 WGS, Italian: 3,984 WES, 3,284 GWAS	European and East Asian	The A allele is more frequent in Italian and the AA genotype confers ACE2 higher expression level.	[1]
		rs112171234, rs12010448, rs143695310, rs1996225, rs200781818, rs2158082, rs4060, rs4646127, rs4830974, rs4830983, rs5936011, rs5936029, rs6629110, rs6632704, rs75979613	ACE2 Genotype Tissue Expression database (GTEx)	East Asian, European, African, South Asian, Mixed American	eQTL variants	[15]
ACE	SARS	ACE I/D	44 cases Hypoxemic/non-hypoxemic	Vietnamese	D allele was more frequent in hypoxemic cases.	[10]
	Septic shock	rs4291, rs4646994	238/242	Chinese	rs4291-TT and rs4646994-DD were associated with disease susceptibility and fatality.	[2]
IL1RN	ARDS	rs315952	three populations with heterogeneous ARDS risk factors	European	C allele was associated with decreased risk	[21]
IL-4	Respiratory tract infectious diseases	rs2070874	2908/6422	General	The T allele was associated with pooled respiratory infections.	[11]
IL-6	ARDS	rs1800796	300/300	Chinese	G allele was a risk factor for ARDS.	[7]
IL-10	ARDS	592C > A rs1800872, 819C > T rs1800871	51 cases at the time of ECMO installation/ 6 hours later	Taiwanese	C allele carriers were associated with higher IL-10 level and poor outcome in severe ECMO-supported ARDS cases.	[22]
		A-1082 G (rs1800896)	211patient/429 healthy subjects	Caucasian	−1082 GA was associated with ARDS susceptibility and mortality.	[23]
	CAP	A-1082 G (rs1800896)	93 cases: 82 survivors/11 dead	Irish	−1082 G was associated with higher expression of the IL-10, and GG genotype was associated with increased severity.	[24]
	Pneumococcal disease	A-1082 G rs1800896	69 cases/50 controls	German	−1082 GG was associated with the highest IL-10 inducibility and septic shock.	[26]
CCL2	SARS	G-2518A rs1024611	932/982	Chinese	GG genotype was associated with the increased risk of SARS.	[7]
CCL5	Bronchiolitis	rs2107538, rs2280788	181 infants/ 536 healthy adults	Brazilian	rs2107538 was associated with bronchiolitis caused by respiratory syncytial virus (RSV).	[19]
TNFα	ARDS	rs1800629	300/300	Chinese	The A allele was a risk factor for ARDS, GG genotype was significantly associated with lower mortality.	[25]
		−308 G > A rs1800629, -863 C > A rs1800630	490 septic pediatric patients /690	Brazilian	−308 GA is protective against the ARDS and sepsis mortality, -863 CA associated with ARDS risk.	[27]
	Sepsis	−308 G > A rs1800629	12,284 cases meta-analysis	Caucasian	This SNP was associated with the risk of sepsis and septic shock, but not mortality.	[28]
IFN-γ	SARS	+874 A > T rs2430561	495/578	Chinese	+874A allele was associated with susceptibility to SARS infection.	[11]
	Pulmonary tuberculosis	+874 A > T rs2430561	4281/5186	General population (Meta-analysis)	+874 A > T is associated with reduced risk of PTB susceptibility in general and Caucasian but not Asian.	[29]
TLR1	Sepsis	−7202 A > G rs5743551	711 / 175	White American	−7202 G was associated with higher TLR1-induced NF-κB activation, higher cell surface TLR1 expression, and increased susceptibility to organ dysfunction, death, and gram-positive infection in sepsis.	[30]
TLR2	Tuberculosis	rs5743708	3262/3124	Different	A allele was associated with TB.	[31]
	Bronchiolitis	rs1898830, rs7656411	181 infants/ 536 healthy adults	Brazilian	Associated with disease severity	[19]
TLR4	RSV	−896 G > A rs4986790	312/356	Finish	A allele was associated with RSV severity.	[20]
	Bronchiolitis	rs4986790, rs1927911	181 infants/ 536 healthy adults	Brazilian	Associated with disease severity	[19]
	Sepsis	rs11536889	152/199	Chinese	C allele was associated with higher risk of sepsis.	[12]

(*continued on next page*)

Table 1 (*continued*)

Gene	Disease	SNP	Sample	Population	Comment	Ref
TLR9	Bronchiolitis	rs352162, rs187084	181 infants/ 536 healthy adults	Brazilian	Associated with disease severity	[19]
CD14	Sepsis	rs2563298	152/199	Chinese	C allele was associated with susceptibility to sepsis.	[18]
	SARS	−159C > T rs2569190	152/198	Chinese	−159CC is associated with severe SARS infection.	[12]
CD55	Influenza	rs2564978	177 severe/248 mild	Chinese	TT genotype was linked with lower transcriptional activity and the disease severity.	[17]
CD209	SARS	−336A > G rs4804803	824 cases	Chinese	−336 AA was associated with higher LDH levels and poor prognosis.	[13]
SFTPB	Influenza	rs1130866	296 severe/185 mild cases	Chinese	CC genotype was associated with severe influenza.	[18]
	CAP	−1580 C > T rs1130866	402 Cases	African American, Asian, White	−1580 C is associated with ARDS, septic shock, and CAP severity.	[15]
VDR	Bronchiolitis	rs2228570	181 infants/ 536 healthy adults	Brazilian	Associated with disease severity	[19]
	RSV	rs10735810	296/113	South African	T allele was associated with the disease susceptibility.	[32]
HLA	Influenza	HLA-A*11, HLA-B*35, HLA-DRB1*10, HLA-DRB1*15	35/35	Assam	Association of HLA alleles with the susceptibility of disease.	[33]
	SARS	HLA-B*4601, HLA-B*5401	33 patients/101 HCW/190 normal control	Taiwanese	HLA-B*4601 was associated with SARS infection severity.	[14]

Acute respiratory distress syndrome (ARDS), expression quantitative trait locus (eQTL), Whole Exome Sequencing (WES), Extracorporeal membrane oxygenation (ECMO), Community acquired pneumonia (CAP), Systemic inflammatory response syndrome (SIRS), Health care workers (HCW) Pneumococcal disease: tuberculosis, influenza, respiratory syncytial virus, SARS-Coronavirus and pneumonia, The respiratory syncytial virus (RSV), lactate-dehydrogenase (LDH).

variants. They reported no indication of the presence of coronavirus S-protein binding-resistant ACE2 mutants in various ethnic groups. The East Asian populations were shown to have higher allele frequencies in the eQTL variants correlated with elevated expression of ACE2 in tissues. Thus, they conclude the role of these variants in the inter-population variability in the risk of SARS-CoV-2 infection or host response to this virus [15].

4. Influenza

Cheng et al. have assessed the role of possible genetic factors that influence the risk of severe H1N1 and H7N9 Influenza infections. They conducted a pilot genome-wide association study (GWAS) and a subsequent assessment of the expression quantitative trait locus (eQTL) data set in the lung tissue. They recognized the GG genotype of rs2070788 in TMPRSS2 as a risk factor of severe H1N1 infection. This variant has been associated with elevated expression of TMPRSS2. They also identified a putative functional SNP namely rs383510 which tags with rs2070788. Functional studies confirmed the regulatory role of rs383510 on TMPRSS2 expression in a genotype-specific mode. Both SNPs were associated with the risk of H7N9 influenza. Taken together, SNPs that increase TMPRSS2 expression are regarded as risk variants for severe H1N1 influenza. Moreover, these variants confer risk of H7N9 influenza [16]. Zhou et al. have shown association between the rs2564978 genotype T/T of CD55 and severe H1N1 infection. They also reported an allele-specific impact on CD55 expression which was attributed to a promoter indel variation located in the complete linkage disequilibrium with rs2564978. CD55 can guard epithelial cells of the respiratory system from complement harm. Moreover, the H1N1 infection enhanced CD55 expression [17]. Moreover, To et al. have reported an association between the C allele of rs1130866 in the surfactant protein B gene (SFTPB) and severe H1N1 disease [18].

5. Respiratory syncytial virus (RSV)

Alvarez et al. reported association between SNP rs2107538 of CCL5 and bronchiolitis caused by RSV. In addition, the rs4986790 of TLR4, rs1898830 of TLR2, and rs2228570 of VDR were regarded as risk factors for progression to death [19]. Löfgren et al. have shown association between the Gly299Gly genotype of TLR4 and protection against severe RSV during the year 2000 epidemics. Yet, they did not verify the association between the Gly299 allele and severe RSV probably due to the effect of environmental and constitutional parameters in determination of susceptibility to severe RSV infection [20].

6. Acute respiratory distress syndrome (ARDS)

Meyer et al. have reported association between the IL1RN SNP rs315952 C allele and lower risk of ARDS in three distinct group of patients with different ARDS risk factors. Notably, this variant was associated higher plasma IL1RA response. IL1RA has been shown to reduce ARDS risk [21]. Liu et al. have shown association between elevated interleukin (IL)-10 levels and two SNPs (-592 C and -819 C) at the promoter region of the corresponding gene. Notably, in patients with ARDS, there was a significant association between IL-10 levels at the time of installation of extracorporeal membrane oxygenation and poor prognosis [22]. Gong et al. also verified the association between the −1082 GG genotype of IL-10 and development of ARDS. Yet, this genotype had a significant interaction with age. Among patients with ARDS, this genotype was associated with reduced severity of disorder on admission as well as deceased mortality and organ damage. Thus, the high IL-10-producing −1082 GG genotype may be related to different risk values of ARDS depending on age [23]. However, in a population of patients with community acquired pneumonia, the −1082 G allele was associated with higher expression of IL-10 and increasing severity of the condition [24]. Ding et al. have demonstrated

associations between the TNF-α rs1800629 A allele and the IL-6 rs1800796 G allele and higher susceptibility to ARDS. Moreover, they reported a protective role for the G allele at MyD88 rs7744 against ARDS. These SNPS have been shown to influence the survival rate of patients as well [25].

Table 1 summarizes the results of studies which appraised the role of SNPs in susceptibility to respiratory disorders or the severity of these conditions.

7. Discussion

With the progression of the COVID-19 pandemic, the need for identification of prognostic biomarkers for susceptibility to severe disease is emerging. The current data about the role of genetic risk factors in the determination of rate of SARS-CoV-2 infection in each ethnic group and the severity of disorder is limited and is not validated by experimental assays. Moreover, several confounding parameters such as the number of tests performed in each country, the structure of the population especially the age distribution, the presence of risk factors for respiratory disorders such as smoking and other environmental factors might be involved in the variability in disease course or prevalence of infection among different ethnic groups [1]. Yet, assessment of the obtained data of association between genetic variants and other relevant viruses such as SARS-CoV might be helpful in this regard. Notably, several genetic loci have been shown to influence the risk of ARDS, a condition which is associated with severe COVID-19 infection. Thus, these genetic variants might also modulate the progression of COVID-19 in the affected patients. These SNPs mostly affect the levels of pro-inflammatory and anti-inflammatory cytokines. However, the results of these studies should be verified in different ethnic groups. Moreover, a number of variants have been associated with more than one of the mentioned disorders. For instance, the rs2070788 of *TMPRSS2* is associated with SARS-CoV2 as well as influenza. Similarly, rs1800629 of *TNFα* is associated with ARDS as well as sepsis. Besides, rs1800896 is associated with higher levels of IL-10, ARDS, severity of community acquired pneumonia (CAP) and septic shock from Pneumococcal diseases. The rs2430561 of *IFN*γ is associated with pulmonary tuberculosis and SARS. Finally, the rs1130866 of *SFTPB* has been associated with severity of CAP and influenza. These data indicate the role of these variants in defining the host response to a these infections which is probably exerted through modulation of immune responses.

There is a necessity for conduction of inclusive investigations that integrate genomic information, epidemiological statistics, and medical records of the clinical manifestation of patients with COVID-19. The final conclusive results are expected to obtain from application of a systems biology approach to assess the data of high throughput sequencing methods. These results permit conduction of an evidence-based risk assessment and the subsequent implementation of preventive and therapeutic modalities in a personalized manner.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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